Title: Advancing Human Neural Models: From Organoids to Physiologically Relevant Systems - Phase Zero studies

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Abstract: Studies of induced pluripotent stem cells (iPSCs) from schizophrenia patients and control individuals revealed that the disorder is programmed at the preneuronal stage, involves a common dysregulated mRNA transcriptome, and identified Integrative Nuclear FGFR1 Signaling as a common dysregulated mechanism. Schizophrenia cerebral organoids (CO) revealed abnormal scattering of proliferating Ki67+ Neural Progenitor Cells from the ventricular zone throughout the intermediate and cortical zones. TBR1 pioneer neurons and reelin, which guides cortico-petal migration, were restricted from the schizophrenia cortex. Maturing neurons were abundant in subcortical regions but depleted in the schizophrenia cortex. Decreased intracortical connectivity was indicated by changes in the orientation and morphology of calretinin interneurons indicating formation of abnormal cortical networks. The watershed hypothesis of schizophrenia asserts that over 200 different mutations dysregulate distinct pathways that converge on unspecified common mechanism(s) that control disease ontogeny. RNA-sequencing of neuron-committed cells (NCCs) differentiated from iPSCs uncovered a dysregulated transcriptome of 1349 mRNAs common to schizophrenia patients bearing different CNV mutations. Data reveal global dysregulation of the developmental and systems mitogenome of the nDNA and mitDNA genes and the formation of aberrant, hyper coordinated gene groups. The Shannon entropy of the interactive nDNAOXPHOS-mtDNAOXPHOS network is significantly increased in schizophrenia NCCs, forming an information-shallow, stabilized OXPHOS system. The functional significance of these changes was explored in a 'Phase Zero' Cerebral Organoid study using combined broadband Vis/near-infrared spectroscopy and electrophysiology. Consistent with the genomic results, pharmacological interventions that enhanced mitochondrial OXPHOS significantly modulated cytochrome-c oxidase activity and electrophysiological measures, indicating partial restoration of mitochondrial bioenergetics and neuronal network function. In conclusion, cerebral organoids can model fundamental features of in utero brain development, including local synaptic E-I ratio and bioenergetics, to complement traditional drug design approaches.



Short Bio: Michal K. Stachowiak received the M.Sc. degree from Nicolaus Copernicus University, Torun, Poland, in 1973, and the Ph.D. degree in neurosciences from the Academy of Medicine, Gdansk, Poland, in 1980. He is currently a Professor with the Departments of Pathology and Anatomical Sciences, Biomedical Engineering, Neuroscience Program, Genetics, Genomics, and Bioinformatics Program, the Director of the Molecular and Structural Neurobiology and Gene Therapy Program, Stem Cells Engraftment and In Vivo Analysis Facility with the State University of New York, Buffalo, USA.

His studies revealed a new global genome-controlling mechanism, Integrative Nuclear Fibroblast growth factor receptor 1 (FGFR1) Signaling (INFS), and a new theory of ontogeny that describes how coordinated gene programs are constructed and executed during development. Since its discovery, several laboratories have investigated targeting INFS for cancer therapy. Professor Stachowiak has made seminal discoveries and developed innovative concepts that have significantly influenced our perception of the genome—its function, structure, and regulation. He advanced the Genome Archipelago model and theory of the Systems Genome as the principles underwriting development, developmental diseases, and different types of cancer. He has integrated human brain organoids, genome, and new optogenomic research (light control of genome functions) to explore new therapies. In particular, he has focused on malformations in neurodevelopmental disorders such as schizophrenia. NIH, NSF, and foundation grants have supported Professor Stachowiak's research. Professor Stachowiak has been a Fulbright Distinguished Professor and Chair of Medical Sciences, and in 2026 became a Foreign Member of the Polish Academy of Sciences.

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